REMARKS

Claims 1-17 and 33 are pending with this amendment. Claims 1-15 and 17 are amended for clarity; support for the amendments is replete throughout the application as filed. Support for new claim 33 is found throughout, see, e.g., paragraph 61. Support for new claim 34 is found throughout the application. The claims were previously rejected for alleged obviousness over various reference combinations and for misjoinder. To the extent that the rejections are applied to the amended claims, Applicants traverse.

THE CLAMED INVENTION

The invention derives from the first ever intravenous delivery of an RNAi agent to achieve a pharmacological effect. This important result provides one of skill with an entirely new approach to suppressing gene expression in vivo, e.g., to treat cancer and other gene mis-regulation diseases. Applicants provided, e.g., the first demonstration of increased cancer survival following delivery of an appropriate RNAi agent in vivo by intravenous delivery. Prior to Applicants' invention, no one had solved the problems of in vivo RNAi agent delivery. The claims relate to new and never previously described compositions that facilitate this new RNAi delivery technology, i.e., a receptor specific nanocontainer that includes an shRNA gene in an interior compartment of a liposome, and a plurality of targeting agents on the exterior of the liposome that target the liposome in vivo. The claimed nanocontainer delivers the shRNA gene in vivo, where the gene is expressed and active.

THE CLAIMS ARE NOT OBVIOUS OVER ZHANG, SHI AND PADDISON

Claims 1, 2, and 7-17 are rejected over Zhang et al. (2002) J. Gene Med. 4:183-194, Shi et al. (2001) PNAS 98:12754-12759 and Paddison et al. (2002) PNAS 1443-1448. The rejection is maintained because Applicant's previous traversal (1) allegedly did not properly consider the references in combination, and (2) because the art in combination allegedly taught the superiority of siRNAs to antisense technologies, motivating the substitution of siRNAs for prior art antisense constructs. Applicant respectfully traverses.

With respect to the argument that Applicant did not previously consider the references in combination, Applicant respectfully notes that the arguments previously

presented are entirely directed at a discussion of the references in combination. The initial discussion of the primary reference, Zhang 2002, was presented to correct manifest technical errors in the prior Examiner's interpretation of the scientific content of the reference (the previous Examiner erroneously argued that the reference taught RNAi constructs, which was factually incorrect). Applicant's corrective discussion was appropriately tied into a discussion of the references in combination at pages 12-13 of Applicant's response.

In any case, the *combination* of references fails to establish the Office's burden of persuasion on the issue of obviousness *vel non*. Indeed, no case for obviousness can properly be made. The combination of references (1) fail to teach the elements of the claim; (2) no specific motivation exists in the prior art for the combination, and (3) perhaps most significantly, no expectation of success in the proposed combination, derived from the prior art, can possibly be made out for the proposed combination.

The Elements Of The Claim Are Not Taught In The Combination Of References

The most basic requirement for establishing obviousness is that the combination of references must teach the elements of the claims. The combination of references plainly fails to meet this most basic of requirements for establishing obviousness.

First, none of the references, separately or in combination, demonstrate in vivo delivery of an RNAi gene. To clarify that the relevant claimed composition has in vivo activity, claim 1 has been amended to recite that the gene within the receptor specific nanocontainer is "expressed in vivo in the mammalian cell following intravenous administration of the nanocontainer to a mammal."

The combination of reference does not show *any* in vivo gene suppression data in mammals, by any mechanism, whatsoever. All of the cited art relating to gene suppression relates to compositions that are, at most, used for in vitro delivery of components. Moreover, **the combination of cited art itself notes that there is a total disconnect between in vitro and in vivo gene delivery technologies**; see, for example Zhang (2002), column 1, paragraph 1, **where the difficulties in extending in vitro gene delivery compositions to in vivo compositions are specifically detailed**, including, e.g., micro-aggregation, sequestration and clearing by the lung, no uptake by target tissues such as the brain, failure of transport across the BBB, lack of stability, rapid clearance, etc. Thus, the

art, in combination, is most properly read as teaching that there is **no** correlation between in vitro and in vivo delivery methods. Further, the problematic features noted in the cited art itself are directly applicable to the only RNAi compositions of the cited combination of art, e.g., the lipofectamine compositions of Paddison (the only RNAi-related reference in the combination of cited art). Thus, given that there is not a single composition in the combination shown to have gene suppression activity in vivo, it is plain that the combination does not remotely provide the basic elements of the claim.

No Specific Motivation for the Combination Exists

The rejection's basic argument is that in vivo gene delivery was shown in the compositions of Shi, that an antisense composition against EGFR is taught in Zhang, and that RNAi (e.g., as per Paddison) and antisense (as per Zhang) have art recognized equivalency of purpose (gene suppression), though, the Action admits, not mechanism of action. In attempting to provide a rationale for the combination of these disparate references, the Action argues that Paddison teaches that there are advantages to double stranded RNAs (for RNAi) over antisense RNAs.

This motivation is drawn from an incomplete consideration of the passages at issue and of the art at issue for the combination. The fundamental rationale offered, essentially that the RNAi of Paddison are taught to work better than antisense, motivating the combination with Zhang and Shi, is not correct. Paddison makes no side by side comparison of the shRNA mechanism with classical antisense RNA inhibition. The Examiner references page 948 of Paddison, where the authors reference prior work in worms, and state, "they found that double-stranded RNA (dsRNA) was much more effective than antisense RNA as an inducer of gene silencing." However, this prior work in worms cannot be translated to mammalian cells, owing to well known differences in RNAi mechanisms in worms and mammals (the claims have been amended to clarify that the relevant cells are mammalian). Thus, Paddison, does NOT teach that shRNA is more potent than classical antisense RNA. The Examiner states that, "the art recognizes the advantages of increased potency and, possibly, stability of dsRNAs, as evidenced by Paddison et al." In fact, the artisan cannot conclude this from Paddison, or the other references in combination, because Paddison shows no comparison of shRNA and antisense RNA. Instead, an artisan would reference works

such as Vickers et al. (2003) (newly cited by the Examiner and discussed in more detail below), who show that siRNA and antisense ODNs have similar activity. As discussed below, Vickers shows that siRNAs and antisense ODNs are equipotent (at least in cell culture following delivery with cationic lipids).

Thus, there is no teaching in the cited combination of references that an RNAi would be more active than the antisense of Zhang et al. in vivo, making any substitution of the Zhang et al. antisense construct for an RNAi construct entirely arbitrary. Indeed, given the admitted differences in mechanism of action between RNAi and antisense, one of skill would not be motivated to substitute an unknown and unspecified RNAi for a known and specified antisense gene repression agent. That is, absent a clear reason to do so, one of skill would make the therapeutic agent that is actually taught in Zhang (antisense against EGFR), rather than attempting to make a different agent (an RNAi against EGFR) that is not actually taught anywhere in the combination of cited references.

No Expectation of Success Existed at the Time of the Invention

Perhaps the most troubling aspect of the rejection is the complete lack of expectation of success that existed at the time the application was filed for the invention at issue. Prior to Applicants' invention, no one had ever successfully delivered RNAi genes intravenously. There was simply no way to know if such an approach would work, absent Applicants' invention. There are numerous potential problems that had to be overcome, including formulation of an appropriate delivery vehicle for in vivo delivery, expression of the RNAi gene in vivo, and production of an active shRNA in vivo (expression of shRNA from a gene requires activity of cellular enzymes such as the "dicer" enzyme for RNAi activity). To assert that one of skill would have had an expectation of success in producing the claimed composition, when none of these problems are remotely addressed by the combination of references is manifestly improper.

In support of the argument that success would have been expected, the Action cites to passages in Zhang et al. (2002) at page 193 arguing that the authors teach that their pegylated liposomes "allow for widespread expression in the brain in vivo." The Action, however, overlooks the "**may**" qualifier of the relevant statements in Zhang et al. The Examiner is respectfully invited to re-read the passage at issue. ***The entire statement in***

Zhang is entirely hypothetical. Zhang (2002) present no in vivo data whatsoever (and neither does Paddison, the only other gene suppression article at issue). The Zhang authors speculate that the pegylated liposomes *may* have in vivo activity. Paddison does not even do this, except with reference to the possibility that transgenic animals might be created. Shi et al. only relates to expression of reporter genes; there is flatly no way at all to know whether adequate levels of delivery and expression could be achieved for gene repression, based on delivery of a reporter—the Examiner is reminded that a reporter gene, by its very nature, is designed to be *easily* detectable, rather than to produce a pharmacological effect (see also, Specification, paragraph 10, where this issue is noted by the Applicant, who is the senior author on the Shi et al. reference). Further, it is plain that the Paddison compositions are *not* likely to have *any* useful activity in vivo, because the cationic lipid formulations they used will simply embolise in the lung. The Zhang passage at issue is, rather plainly, a *hoped* for activity of the liposome system at issue (which did not include an shRNA gene). One cannot base an expectation of success on a speculative statement in the prior art that a particular composition "may" have an activity at issue. In essence, the entire argument bootstraps expectation of success for the claimed in vivo active composition—which is plainly not taught anywhere in the prior art—based on a speculative statement that a different composition may (or may not!) have useful in vivo activity. This is entirely insufficient to demonstrate expectation of success.

Here again, the rejection also fundamentally ignores the profound mechanistic differences between shRNA and other types of genes. While the Examiner correctly notes that there are mechanistic differences, these are dismissed in view of "art recognized" equivalence in the purpose of shRNA as compared to, e.g., antisense. Applicants agree that shRNA and antisense can both be used for repressing gene expression. However, this is irrelevant to the issue of expectation of success for the *claimed* composition. If the mechanisms by which these different types of therapeutic agents act are entirely different (and they plainly are), then the fact that one type (antisense) is effective against a gene (in vitro) cannot serve as a proxy for showing that the other type (shRNA) would also be effective (in vivo).

Briefly, shRNA is processed and acts in a cell using a completely different mechanism of action (RNA interference, or "RNAi") as compared to a classical anti-sense RNA molecule. To achieve RNAi from an expressed plasmid RNA encoding an shRNA, the plasmid DNA must be delivered to the nuclear compartment, the DNA must then transcribed into an shRNA in the nucleus, followed by export of the shRNA to the cytoplasm, where it is processed to the RNA duplex by cellular enzymes (e.g., Dicer) to produce the siRNA. Further, the action of the siRNA on mRNA leads to specific cleavage of the mRNA. In contrast, an antisense molecule simply enters the cytoplasm, without entry into the nucleus, where it hybridizes to the target mRNA, which then triggers RNAse H cleavage. Thus, there is simply no way of inferring expectation of success from anti-sense to shRNA technologies. Indeed, prior to the present application, there had been multiple demonstrations of antisense gene therapeutic effects on cancers, similar to Zhang (2002); however, there was not a single previous demonstration of an increase in survival from cancer of any type with intravenous shRNAi gene therapy, such as described in the specification (see specification, figure 2). Given that shRNA was known in general well prior to Applicants' invention, this provides strong extrinsic evidence for non-obviousness of the claimed invention.

The rejection must be withdrawn.

THE INVENTION IS NOT OBVIOUS OVER ZHANG, PADDISON, SHI, BENNET, TUSCHL, BASS AND VICKERS

The Action cites Zhang et al. (2002), Shi et al (2001), and Paddison et al (2002) essentially for the reasons noted above, further offering Bennet et al ('269 patent), for the proposition that oligonucleotides targeted to EGFR can reduce EGFR expression; Tuschl et al. for the argument that any double stranded RNAi can be made to inhibit mammalian gene expression; Bass et al. for the argument that RNAi is more robust than antisense inhibition; and Vickers et al. for the argument that antisense and RNAi targets are largely overlapping. Applicants respectfully traverse.

As an initial matter, in making this rejection, the Action improperly equates five different types of antisense drugs and also improperly equates in vitro and in vivo methodologies and compositions.

General Comment Regarding 5 Different Types Of Antisense Drugs:

Part of the confusion with the subject examination is that many different gene knock down technologies are equated in the rejection. These include the following:

(a.) An antisense RNA. An antisense RNA that is several hundred nucleotides in length can be an antisense agent. The antisense RNA is produced inside a target cell, following delivery of an exogenous plasmid. The therapeutic efficacy of antisense RNA requires the development of an effective plasmid DNA delivery system.

(b.) An antisense oliodeoxynucleotide (ODN) is a short 15-mer to 30-mer DNA polymer that acts as an antisense agent by targeting a specific RNA sequence. The therapeutic efficacy of antisense ODN requires the development of an effective ODN delivery system.

(c.) A ribozyme is an antisense agent, and is a short single stranded RNA molecule that is delivered to the cell. The therapeutic efficacy of ribozymes requires the development of an effective plasmid DNA delivery system.

(d.) A short interfering RNA (siRNA) is a short 19-mer to 30-mer duplex of RNA that is delivered to the cell. The use of siRNAs is a form of RNA interference (RNAi). The therapeutic efficacy of siRNA requires the development of an effective siRNA delivery system.

(e.) A short hairpin RNA (shRNA) is a short single stranded RNA that is encoded by a plasmid DNA, and following transcription in the cell is processed into an RNA duplex that is similar in structure to an siRNA. The use of shRNAs is a form of RNAi. The therapeutic efficacy of shRNA requires the development of an effective plasmid DNA delivery system.

These methods are "art equivalent" only insofar as each approach attempts to knockdown the expression of a target gene. Plainly, each of the above 5 antisense approaches work by completely different molecular mechanisms and present vastly different issues for administration. The present application only applies to compositions for 1 of the above 5 antisense approaches (e.), i.e., the delivery and in vivo expression of shRNA genes.

General comment on relationship between RNAi composition for cell culture vs compositions for intravenous RNAi:

In all 5 of the above cases, the delivery of the antisense agent, including RNAi agents, to a cell in culture is very simple. The artisan simply mixes the RNA or DNA with a cationic polymer such as lipofectamine, or any number of similar cationic polymers. The anionic DNA and the cationic polymer form an aggregate in physiological saline, and this aggregate is taken up by the cell in culture via phagocytosis. However, the same cationic polymers that are so effective in culture do not work in vivo. This is because the aggregates embolise in the first capillary bed encountered in vivo after an intravenous injection, which is the pulmonary circulation (in the lung). Therefore, one limiting factor in the development of intravenous RNAi is the vivo delivery system. Nothing in the combination of prior art enables the artisan to solve the fundamental problem of how to achieve intravenous RNAi effects in vivo. This is accomplished in the present specification, which describes the first pharmacologic effect with intravenous RNAi gene agents in vivo ever demonstrated.

The References In Combination Still Fail to Teach the Claimed Invention

The fundamental failure of the combination of Zhang et al, Shi et al. and Paddison et al. to teach the limitations of the claims is discussed in detail above. For convenience, the remaining references are discussed in combination in the same order presented by the Examiner.

Bennet is further combined with Zhang et al, Shi et al. and Paddison et al. for the proposition that Bennet teaches the knockdown of EGFR expression. Applicants note that this reference is limited to (at most) the delivery of oligonucleotides in vitro. This fails to provide any evidence relating to the claimed invention, which includes, e.g., "a receptor-specific nanocontainer capable of delivering a gene to a cell in vivo by intravenous delivery, wherein the gene is expressed in the cell in vivo to produce the short hairpin RNA in the cell." As noted above, the delivery issues surrounding oligonucleotides and plasmids are utterly dissimilar; moreover, all data in Bennet is in vitro, providing no evidence for in vivo activity (again, the in vitro methods of Bennet result in an embolism in vivo, and are, thus, utterly inapplicable). Thus, Bennet, in combination, fails to remedy the deficiencies of the combination of Zhang, Shi and Paddison, already discussed in detail.

Parenthetically, there are also technical difficulties in interpreting Bennet, even for the limited purposes noted. Bennet references the work of Wang et al (1995), who show that antisense ODNs encapsulated in folate targeted pegylated liposomes knock down cell proliferation in culture. However, Wang et al provide no data that the EGFR gene or protein is knocked down in this model. Therefore, Wang et al provide no support that the anti-EGFR ODN actually even worked via an antisense mechanism. They only show an inhibition of cell proliferation. Per Wang et al., this inhibitory effect was transient and completely lost after 4 days in culture. Thus, it is arguable whether Bennet even provides the in vitro results supposed in the rejection; in any case, even if they do, these methods result in an embolism in vivo, and add nothing to the combination of references.

Tuschl et al. is considered by the Examiner to be a "complete blueprint" for the design, synthesis and use of shRNA. In fact, this is an overstatement of the relevance of the reference to the claimed invention. Tuschl only provides evidence for RNAi mechanisms *in cultured cells*. Tuschl provides no data at all showing that shRNA can be delivered to mammalian organs in vivo, or any compositions for achieving this, e.g., as described and claimed in the subject application. Tuschl simply does not teach the artisan *how* to implement RNAi effects in vivo. The mere suggestion that this *might* be possible, as outlined in Tuschl paragraphs 31-33, does not actually teach the artisan *how* to achieve intravenous RNAi agent delivery and expression in vivo. In contrast, the specification teaches specific formulations that enable the artisan to achieve intravenous RNAi in vivo. Thus, the combination of Zhang, Shi, Paddison, Bennet and Tuschl is still completely deficient in showing what the composition of a nanocontainer that can deliver an RNAi gene by intravenous administration would be.

Bass and Tuschl are both cited for the proposition that siRNA works better than previous antisense methods. Applicants note that even if this were correct (it is not, i.e., the references are badly flawed, as discussed in more detail below), it would still fail, in combination with the other references noted, to provide the claimed composition. Even if the prior art in combination were read to show the superiority of RNAi (in vitro, obviously, as there is no comparative in vivo gene suppression data in mammals for any reference in the

combination, whether antisense or RNAi), this still fails to provide any teaching of the claimed composition at issue.

Vickers is cited for the proposition that there is a correlation between targets for antisense and RNAi. Here the Examiner has improperly equated siRNAs and shRNAs, i.e., Vickers relates to a comparison of antisense oligonucleotides and siRNAs, delivered to cells in culture—that is, with a cationic lipid, i.e., an approach that flatly does not work in vivo. Thus, the combination of Zhang, Shi, Paddison, Bennet, Tuschl, Bass and Vickers simply does not teach the specific composition being claimed. Instead, at least 4 different types of gene inhibition technologies are taught in the references (none of which are the 5th approach of delivering shRNA genes used by Applicants, as discussed above), with all of the gene suppression data in all of the combined references being limited to effects shown in vitro. Without any actual teaching of a composition for intravenous in vivo RNAi, e.g., to an organ, the combination of the prior art cannot establish even the elements of the claimed invention.

The combination of References is Unmotivated

The Action's argument for the combination of references is essentially an argument that Bass and Tuschl teach the superiority of RNAi, as compared to antisense, as a gene inhibition mechanism, justifying the combination of disparate references that relate to delivery of antisense oligonucleotides in vitro (Bennet, Vickers), RNAi in vitro (Vickers, Tuschl, Paddison), delivery of genes for antisense RNA in vitro (Zhang), and delivery of β-galactosidase and luciferase genes in vivo (Shi). There are several difficulties with this argument.

First, neither Bass nor Tuschl actually show any superiority of RNAi as compared to antisense technologies (and, of course, all of the information in these references is limited to in vitro data). The 2001 Bass reference is a short, non-peer-reviewed summary of the primary Elbashir et al (2001) publication in Nature (vol 411, p 494-498, attached) regarding short interfering RNA (siRNA) from the lab of Tuschl. The Examiner re-states a position held by Bass, which restates a position held by Tuschl, which is not supported at all by the data. The Examiner states, "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments." This

statement is drawn from Bass, who states, "as Tuschl and colleagues show, even in mammalian cells, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments." This statement, made by Bass in a lay audience summary article, is derived from Elbashir and Tuschl. Elbashir states that, "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene-targeting experiments.[20]" (page 496, column 1). The statement by Elbashir is inaccurate. Elbashir only shows that siRNAs against an exogenous gene, luciferase, are effective at 25 nM. In support of their argument for increased potency of RNAi, they cite a single reference, Macejak et al (2001), which relates to ribozymes, and not to RNAi at all. Moreover, Macejak show inhibition of endogenous gene expression at 50 nM ribozyme using the same type of cationic lipid RNA delivery system used by Elbashir. One can conclude from Bass and Elbashir that siRNAs and ribozymes are equally effective in cell culture, but this is not particularly relevant to the present invention.

Further, Vickers, also cited in the Action, ***directly contradicts*** the arguments made with respect to superior properties for RNAi, and does so with **actual data**. That is, Vickers shows that at least siRNAs and antisense oligonucleotides are equipotent in cell culture, following in vitro delivery with cationic lipids. Thus, the argument that RNAi works better than antisense is directly refuted by the *only* data-supported comparison provided in the references cited in the combination.

There was No Expectation of Success

Here again, no expectation of success can possibly be found in the references of the combination. None of the art cited has an example of gene suppression in vivo in a mammal, whether by antisense or RNAi. Moreover, the cited art itself (e.g., Zhang, page 158, column 1) expressly indicates that in vitro results cannot be extrapolated to an in vivo setting. Thus, none of the results in any of the references of the combination can be extrapolated to the claimed composition to show any expectation of success whatsoever for the claimed composition. None of the art demonstrates that gene suppression can even be achieved in an in vivo setting in a mammal, or compositions for doing so. The problems of in vivo shRNA gene delivery, shRNA gene expression and cellular processing of shRNA to

provide RNAi, in an in vivo setting, simply are not even addressed by the combination of references.

Furthermore, the Examiner's argument that RNAi can routinely be substituted for antisense is a considerable oversimplification of the issues involved in the subject case. There had been several attempts at achieving RNAi in mammalian cells that had failed in the prior art. See, e.g., Paddison, page 951, column 1. Although Paddison achieved RNAi in certain cultured mammalian cells, this was certainly not a demonstration that such a mechanism was even available in, e.g., any organ that is, e.g., a therapeutic target of interest a mammal. It is well known that cells in culture, particularly those that have been clonally selected over many generations, have many biochemical and gene regulatory differences (e.g., immortality, etc.) that are not mirrored in the cells of, e.g., an organ in vivo. To the extent that any of the data in any of the combined references relates to mammalian cells at all, the cells that had previously been tested for RNAi activity were precisely these types of cultured cells, i.e., HEK293 cells, HeLa cells, COS-1 cells, NIH 3t3 cells, and IMR90 cells (e.g., Paddison, p. 293). Without actually having examples of in vivo expression of shRNA in organs of an intact animal, there was flatly no way that one of skill could predict what would happen, with any "reasonable expectation" of success.

Finally, it is worth noting that **the Patent Office itself has made public presentations as to patentability issues raised by in vivo RNAi that directly contradict the Examiner's arguments regarding expectation of success**. For example, Irem Yucel, Ph.D., SPE for Art Unit 1636 presented a public seminar regarding the distinctions between antisense and RNAi, as part of a "Hot Topics in Biotechnology Patent Law," seminar by Group 1600 (Sept 9, 2004, in Milbrae, CA). SPE Yucel specifically noted that there was a *low* expectation of success for *in vivo* RNAi applications (largely due to the delivery problems that are overcome by Applicant's invention!). A copy of the relevant slide from this public presentation is submitted herewith.

The rejection must be withdrawn.

ELECTION/RESTRICTIONS

Applicants stand on their previous arguments that the restriction requirement is a completely improper rejection of the claims as filed for misjoinder. As previously noted,

Applicants are entitled to traverse the rejection for misjoinder outside of the auspices of restriction practice. Applicants maintain that the rejection of the claims must be withdrawn as a facially improper misjoinder rejection.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, **a telephone interview with the Examiner is hereby requested**. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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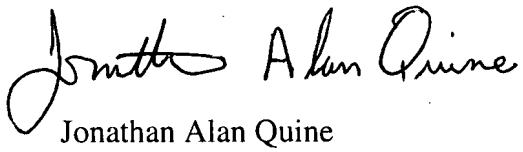
Respectfully submitted,



Jonathan Alan Quine
Reg. No: 41,261

Attachments:

1) A petition to extend the period of response for 2 months;
2) A transmittal sheet;
3) A fee transmittal sheet;
4) A copy of a page from a slide set presented at the Symposium for Hot Topics in Biotechnology Patent Law by USPTO Technology Center Group 1600, from a talk entitled "Antisense and RNAi" by Irem Yucel, Ph. D., SPE, Art Unit 1636, presented in Millbrae, CA on Sept. 9, 2004;
5) A Request for Continued Examination; and,
6) A receipt indication postcard.

RNAi Patentability Issues

35 U.S.C. 103 - Obviousness

- **Expectation of Success**
  - expectation of RNAi gene silencing highly likely for target sites identified as accessible to antisense inhibition (see Vickers et al. (J. Biol. Chem.) 278: 7108-7118, 2003)
  - low expectation of success for in vivo applications
  - low expectation for specific target sequences which are not identified
  - identification of some sequence as appropriate target should be provided, e.g. known antisense target